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| ART UNIT | PAPER NUMBER |
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DATE MAILED: 09/10/92

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 17 Jan 1992 and 13 Aug 1992 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

**Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:**

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice re Patent Drawing, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

**Part II SUMMARY OF ACTION**

1. ☑ Claims 1-59 are pending in the application.
   Of the above, claims 1-24, 29-41, and 56-59 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 25-28 and 42-55 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

**EXAMINER'S ACTION**

PTOL-326 (Rev. 9-89)

The application should be reviewed for errors.

Applicant's election of Group IV, claims 25-28 and 42-55 in Paper No. 14 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide a reasonable written description, enablement and best mode for practicing the claimed invention. The transgenic non-human animal used in the method is not disclosed as to any particular characteristics and there is no example descriptive of the process defined by claims 49-55. Here, the specification at pages 1-2 creates doubt as it indicates that manipulation is impaired due to inability to control site of integration, number of copies, temporal expression, and the like. Given these difficulties how is the non-human transgenic mammal used in the process made so that the FLP target site is not at some random location and what gene is it located in? Before a specific gene can be targeted by DNA which contains the FLP recombination target site (FRT), it must have a specific site for recombination already in the genome of the host. Here, the specification has not indicated a particular transgenic animal where the location of the FLP sites are initially at specific sites predetermined by the user. Note that page 9, lines 10-14 refers to the non-human transgenic animal with the FLP site but does not indicate how the specificity of the placement of the site in the genome is determined or produced, i.e. how is the FLP site for the animal specifically targeted to a specific gene and what portions of that gene are best suited to or for integration of the FLP recombination site? Inasmuch as the non-human

mammal contains cells per se, and the FLP site is in the cells, the specification has not provided enabling description for site specific integration of the DNA coding for the FLP site (i.e. the target for the DNA which recombines at the FLP site).

Claims 25-28 and 42-55 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 25-28 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to host cells in vitro. While applicant indicates that the treatment for humans is contemplated, page 15, lines 24-29 indicates that no claim is to be directed to genetically modified human hosts, however, the "host organism" in claim 25 also encompasses humans and "contemplates" is not an enabling written description. As to claims 49-55, they require the use of a non-human transgenic mammal, however, that method of producing the mammal used in the process of claim 49-55 is not disclosed in a manner that is reproducible (page 5) and there is no written description of an example that indicates how that mouse set forth at page 5 is made. Here, where the organism upon which the process of claims 49-55 is to be practiced is not disclosed in such a manner as to be available, the method is unpracticable. Amendment of the claims with "cultured transformed host cells" as a replacement for "host organism" (claim 25) and "mammalian cell wherein the genomic DNA of the cell contains at least one FLP recombination target site" is suggested. See MPEP 706.03(n) and 706.03(z). Amendment of the independent claims 29, 42, and 49 is suggested below.

Claims 25-28 and 42-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 (lines 6 and 15) recites "the subject" and "said subject" which is unclear because "subject" has several definitions, one of which is "a person under the rule of another" or as a part of speech. Replacement of "host organism" (claim 25, line 2), "the subject" (line 6) and "said subject"

(line 15) with "non-human host cell" is suggested. Claims 42 and 49 are vague and indefinite for depending from claims 29 and 35, respectively which are withdrawn from consideration. It is suggested that claim 42 incorporate the terminology "mammalian cell wherein the genomic DNA of the cell contains at least one FLP recombination target site" as a replacement for "cell according to claim 29" and that claim 49 incorporate the terminology "transgenic non-human mammalian cell which contains at least one FLP recombination target site in the genome of said mammalian cell" as a replacement for "a host according to claim 35". In claims 43-44 and 50-51, it is not clear which portion of the gene(s) is referred to by the recitation of "within at least a portion of one or more" (claims 43 and 50); in claims 44 and 52, the recitation of a "... second portion ..." and "... at least a portion ..." is unclear. Where is the "first portion" and what defines "at least a portion"? See the specification at page 13.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action :

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

"A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where

the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 25-28 are rejected under 35 U.S.C. 102 (b) as being anticipated by Golic et al. which discloses site specific recombination in D. melanogaster using DNA coding for FLP and FRT (see at least pages 499 and 507) where it is indicated that FRT bearing plasmids can be directed to the site of an FRT already resident in the genome for germline transformation which would have resulted in a process for producing the host organism. The step of mating the flies (page 500), is a step of introducing the cells which are the male or female gametes into the subject where the subject is the other D. melanogaster gamete which after fertilization becomes a transgenic fruit fly.

Claims 25-28 and 42-55 are rejected under 35 U.S.C. 103 as being unpatentable over Sauer (U.S. '317) taken with Golic et al.

Sauer teaches site specific recombination of mammalian cells (col 14+) using plasmids with the DNA coding for the cre and lox (cols 1, 6-7). Where Sauer does not explicitly disclose the use of DNA coding for FLP and FRT, it would have been obvious to one of ordinary skill in the art to use DNA coding for FLP and FRT in vectors for transforming D. melanogaster because Golic et al. discloses site specific recombination in D. melanogaster with DNA coding for FLP and FRT (see at least pages 499 and 507) where it is indicated that FRT bearing plasmids can be directed to the site of an FRT already resident in

the genome suggesting its use for germline transformation which would have resulted in a transgenic animal and further indicate that "we expect the it will work in other organisms as well" which would have motivated one of ordinary skill in the art to combine the teachings of Sauer which discloses at cols 14+, site specific recombination in mammalian cells (mouse) where the combination of the Sauer and Golic et al. references would have resulted in a method for site specific recombination in mammalian cells or in transgenic animals. Moreover, where both Sauer and Golic et al. teach that the DNA for the FLP and FRT are from yeast, Sauer teaches at col 5, mating the yeast of opposite mating types which contain the plasmids with the DNA for the FLP and FRT which is a step of introducing the cells produced by the step (i) and (ii) of claim 28 into the subject where the subject is another yeast cell and where Golic et al. disclose mating the flies (page 500), it is a step of introducing the cells which are the male or female gametes into the subject where the subject is the other D. melanogaster gamete which after fertilization becomes a transgenic fruit fly. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was a whole, clearly prima facie obvious.

Claims 25-28 are rejected under 35 U.S.C. 103 as being unpatentable over Sauer (U.S. '317) taken with Golic et al. as applied to claims 42-55 above, and further in view of Palmiter et al. as directed to the "said subject" being a transgenic animal.

Sauer and Golic et al. are applied as indicated above and where Golic et al. indicates expectation of success as indicated above, one of ordinary skill in the art would have found it obvious to combine the teachings in the Palmiter et al. reference whcih discloses introduction of the transforming DNA into totipotent teratocarcinoma cells or embryonic stem cells which can be introduced into the developing embryo by aggregation of the cells. Here, where Sauer taken with Golic et al. disclose the plasmids with the FLP and FRT DNA for site specific recombination, it would have been obvious to one of ordinary skill in the art given that Golic et al. indicate that "we expect the it will work in other organisms as well", to modify the process by using

totipotent teratocarcinoma cells or embryonic stem cells as disclosed by Palmiter et al. which are later aggregated with the developing mouse embryo. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was a whole, clearly prima facie obvious.

No claim is allowed.

The O'Gorman et al. reference is cited as of interest as disclosing the entire invention, however, of note is the difference in authorship as compared to the presently named inventors.

An inquiry concerning this communication should be directed to Christopher Low at telephone number (703) 308-0196.

CSFL
04 Sep 1992

Christopher S.F. Low

CHRISTOPHER S.F. LOW
PATENT EXAMINER
GROUP 180